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Mitchell A. Avery, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of North Dakota
Dept. of Chemistry
Box 8138, University Station
Grand Forks,ND 58202

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This is a final report for a grant that was transfered, at the end of its first year, with the P.I. upon a change of Universities. Therefore, it encompasses only one year of work dealing with computer modeling of antimalarial drugs. We have developed a very reliable computer aided approach to defining the antimalarial activities of drugs related to the natural product, artemisinin.

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"DIRECTED SYNTHESIS OF NEW ANTIMALARIALS USING COMPUTER AIDED DRUG DESIGN"

FINAL TECHNICAL REPORT

MITCHELL A. AVERY, PH.D.

OCTOBER 24, 1995

U. S. ARMY RESEARCH OFFICE

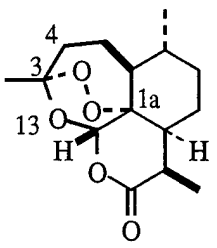
GRANT NUMBER: DAAL 03-92-G-0353

UNIVERSITY OF NORTH DAKOTA

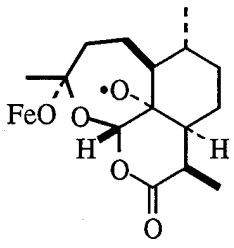
3D-Quantitative Structure-Activity Relationship Studies of Artemisinin Analogs: Comparative Molecular Field Analysis.

Abstract: This is a final report for a grant that was transfered, at the end of its first year, with the P.I. upon a change of Universities. Therefore, it encompasses only one year of work dealing with computer modeling of antimalarial drugs. We have developed a very reliable computer aided approach to defining the antimalarial activities of drugs related to the natural product, artemisinin.

Much effort has been expended to develop new antimalarial drugs based on the natural product lead structure, (+)-artemisinin **1**.[1,2,3] The unusual peroxy moiety of this cadinane sesquiterpene was found to be essential for antimalarial activity,[4] and prompted by Meshnick's observation of the reaction of hemin with **1**,[5] Posner has suggested that carbon-centered radical chemistry surrounds the mode of antimalarial action of this class of drugs.[6] In Posner's *in vitro* studies, cleavage of the oxygen-oxygen bond of structures such as **1** by Fe(II) leads to an intermediate oxygen radical (e.g. **2**) which then abstracts, in an intramolecular 1,5-fashion, a hydrogen atom from C-4.[7] The fate of this resultant carbon radical **3** is as yet not understood, although Meshnick's group continues to study the biochemical course of reaction of **1** *in vivo*.[8] The importance of intermediate carbon radicals in the mechanism of action of simpler artemisinin analogs has also been demonstrated by Jefford.[9]



1, (+)-Artemisinin



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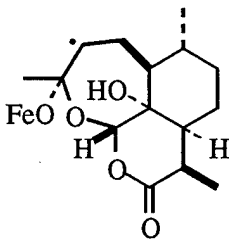

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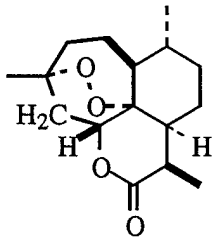

4, (+)-13-Carbaartemisinin

Structure-activity relationship studies continue to accumulate in the artemisinin area. For example, the peroxide moiety is accepted as essential for activity while the lactone carbonyl can be removed[10,11,12,13] or a lactam ring can be substituted for the customary lactone ring without detriment to antimalarial activity.[14,15,16] The effect of ring substitution has been examined at several positions of both the intact tetracyclic system[17,18] as well as many tricyclic analogs.[19,20,12,21] While the antimalarial activity of numerous peroxides has been explored,[22,23] replacement of the non-peroxidic trioxane ring oxygen atom in artemisinin by a methylene unit had not been carried out until recently.[24] Our group has attempted to use this burgeoning analog data to construct a pharmacophore model that could predict the activities of new antimalarial analogs of artemisinin. We have used a 3D quantitative SAR modeling approach refered to as CoMFA or comparative molecular field analysis. Simplistically, CoMFA mathematically correlates steric and electrostatic parameters in 3D space about a molecular dataset with a target property, which is in this case, antimalarial test data. The validity of a resultant correlation is statistical in nature, with r^2 values being reported. Crossvalidation is also employed, a process whereby the analogs are randomly excluded in sets or separately, from the calculation. How well the resulting equations predict the activity of the excluded molecules is reflected in the crossvalidated r^2 (r^2_{cross}). An r^2_{cross} of 0.9 translates very roughly to an ability of the model to closely predict about 90% of the activities.

From a chronological perspective, we began development of a comparative molecular field analysis (CoMFA) of artemisinin analogs in 1992. Our earliest efforts are chronicalled in a recent article published in the J. Medicinal Chemistry *36* , 4264 (**1993**) dealing with substituents mainly at the C-9 position. We found good correlations with excellent statistical parameters (r^2_{cross} = 0.857, etc.) for a dataset of about 40 analogs, but the CoMFA model suffered from limited utility due to the lack of information about other positions in the molecule. In other words, we had good predictive ability but only in regards to C-9 substituted analogs of artemisinin. In a slightly later iteration published as a book chapter in Trends in Organic Chemistry *4,* 413 (**1993**), we incorporated some of the N-11 aza analogs and a number of seco-analogs of artemisinin. The final dataset was still around 40 compounds (r^2_{cross} = 0.648, etc.), and we still required much additional SAR information for inclusion into more of a "global" CoMFA model.

In order to correct this deficiency, we then began to study the addition of other unpublished analogs prepared in our hands, as well as compounds from the literature. With a dataset of 83 analogs, we obtained r^2_{cross} = 0.747. This model was useful in predicting new structures appearing in the literature. These results were published as MEDC No. 240, 207th ACS meeting (San Diego, March **1994**).

In the interviening year, we have significantly expanded our CoMFA model. Initially, we added a number of new compounds of our own as well as virtually all of those which had compatable bioassay from the literature into a total database of 162 compounds. The first run gave after deletion of outlyers, r^2_{cross} = 0.836 (optimum component = 5, database = 153 analogs), conventional r2 = 0.924. This was considered to be an excellent CoMFA model.

We have since done some fine-tuning as well as addition of new analogs. We now have corrected analogs for differences in MW with relative potencies now being calculated by:

Relative Potency = [IC50 artemisinin/IC50 artemisinin analog]X[MW analog/MW artemisinin]x100

The newest iteration of the CoMFA model has r^2_{cross} = 0.840 (optimum component = 5, database = 154 analogs), conventional r^2 = 0.905. We are using this model to conduct design efforts.

Future modeling efforts will take into account different methods of calculating charges for the CoMFA as well as inclusion of Log P data into the CoMFA correlation, and will of course attempt to incorporate any new analogs as they become available. We are particularly interested in including information from analogs derived at C-4 and C-5, and eventually the cyclohexyl portion of the analog. This shall complete the needed SAR and we should be able to finalize our model and begin to do design in earnest.

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